ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zerit 15 mg hard capsules
Zerit 20 mg hard capsules
Zerit 30 mg hard capsules
Zerit 40 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zerit 15 mg hard capsules
Each hard capsule contains 15 mg of stavudine.

Excipients with known effect
Each hard capsule contains 80.84 mg of lactose anhydrous.
Each hard capsule contains 40.42 mg of lactose monohydrate.

Zerit 20 mg hard capsules
Each hard capsule contains 20 mg of stavudine.

Excipients with known effect
Each hard capsule contains 121.30 mg of lactose anhydrous.
Each hard capsule contains 60.66 mg of lactose monohydrate.

Zerit 30 mg hard capsules
Each hard capsule contains 30 mg of stavudine.

Excipients with known effect
Each hard capsule contains 121.09 mg of lactose anhydrous.
Each hard capsule contains 60.54 mg of lactose monohydrate.

Zerit 40 mg hard capsules
Each hard capsule contains 40 mg of stavudine.

Excipients with known effect
Each hard capsule contains 159.06 mg of lactose anhydrous.
Each hard capsule contains 79.53 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Zerit 15 mg hard capsules
The hard capsule is red and yellow, opaque and imprinted with “BMS” over a BMS code “1964” on one side and “15” on the other side.

Zerit 20 mg hard capsules
The hard capsule is brown, opaque and imprinted with “BMS” over a BMS code “1965” on one side and “20” on the other side.

Zerit 30 mg hard capsules
The hard capsule is light and dark orange, opaque and imprinted with “BMS” over a BMS code “1966” on one side and “30” on the other side.

Zerit 40 mg hard capsules
The hard capsule is dark orange, opaque and imprinted with “BMS” over a BMS code “1967” on one side and “40” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected adult patients and paediatric patients (over the age of 3 months) only when other antiretrovirals can not be used. The duration of therapy with Zerit should be limited to the shortest time possible (see section 4.2).

4.2 Posology and method of administration

The therapy should be initiated by a doctor experienced in the management of HIV infection (see also section 4.4).

For patients starting therapy with Zerit, the duration should be limited to the shortest time possible followed by a switch to an alternative appropriate therapy whenever possible. Patients continuing treatment with Zerit should be assessed frequently and switched to an alternative appropriate therapy whenever possible (see section 4.4).

Posology

Adults: the recommended oral dosage is

Patient weight	Zerit dosage
< 60 kg	30 mg twice daily (every 12 hours)
≥ 60 kg	40 mg twice daily (every 12 hours)

Paediatric population

Adolescents, children and infants over the age of 3 months: the recommended oral dosage is

Patient weight	Zerit dosage
< 60 kg	1 mg/kg twice daily (every 12 hours)
≥ 60 kg	adult dosing

The powder formulation of ZERIT should be used for infants under the age of 3 months. Adult patients that have problems swallowing capsules should ask their doctor about the possibility of changing to the powder formulation of this medicine.

Please refer to the Summary of Product Characteristics of the powder formulation.

Dose adjustments

Peripheral neuropathy: if symptoms of peripheral neuropathy develop (usually characterised by persistent numbness, tingling, or pain in the feet and/or hands) (see section 4.4) patients should be switched to an alternative treatment regimen, if appropriate. In the rare cases when this is inappropriate, dose reduction of stavudine may be considered, while the symptoms of peripheral neuropathy are under close monitoring and satisfactory virological suppression is maintained. The possible benefits of a dose reduction should be balanced in each case against the risks - which may result from this measure (lower intracellular concentrations).

Special populations

Elderly: Zerit has not been specifically investigated in patients over the age of 65.

Hepatic impairment: no initial dosage adjustment is necessary.

Renal impairment: the following dosages are recommended

Patient weight	Zerit dosage (according to creatinine clearance)	
	26-50 ml/min	≤ 25 ml/min (including dialysis dependence*)
< 60 kg	15 mg twice daily	15 mg every 24 hours
≥ 60 kg	20 mg twice daily	20 mg every 24 hours

* Patients on haemodialysis should take Zerit after the completion of haemodialysis, and at the same time on non-dialysis days.

Since urinary excretion is also a major route of elimination of stavudine in paediatric patients, the clearance of stavudine may be altered in paediatric patients with renal impairment. Although there are insufficient data to recommend a specific dosage adjustment of Zerit in this patient population, a reduction in the dose and/or an increase in the interval between doses proportional to the reduction for adults should be considered. There are no dosage recommendations for paediatric patients under the age of 3 months with renal impairment.

Method of administration

For optimal absorption, Zerit should be taken on an empty stomach (i.e. at least 1 hour prior to meals) but, if this is not possible, it may be taken with a light meal. Zerit may also be administered by carefully opening the hard capsule and mixing the contents with food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Co-administration with didanosine due to the potential for serious and/or life-threatening events notably lactic acidosis, liver function abnormalities, pancreatitis and peripheral neuropathy (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Stavudine therapy is associated with several severe side effects, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity. Given these potential risks, a benefit-risk assessment for each patients should be made and an alternative antiretroviral should be carefully considered (see *Lactic acidosis, Lipoatrophy,* and *Peripheral neuropathy* below and section 4.8).

Lactic acidosis: lactic acidosis, usually associated with hepatomegaly and hepatic steatosis has been reported with the use of stavudine. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, renal failure, or motor paralysis.

Lactic acidosis generally occurred after a few or several months of treatment.
Treatment with stavudine should be discontinued if there is symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
Caution should be exercised when administering stavudine to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.
Patients at increased risk should be followed closely (see also section 4.6).

Liver disease: hepatitis or liver failure, which was fatal in some cases, has been reported. The safety and efficacy of stavudine has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

In the event of rapidly elevating transaminase levels (ALT/AST, > 5 times upper limit of normal, ULN), discontinuation of Zerit and any potentially hepatotoxic medicinal products should be considered.

Lipoatrophy: on the basis of mitochondrial toxicity stavudine has been shown to cause loss of subcutaneous fat, which is most evident in the face, limbs and buttocks.

In randomized controlled trials of treatment-naive patients, clinical lipoatrophy developed in a higher proportion of patients treated with stavudine compared to other nucleosides (tenofovir or abacavir). Dual energy x-ray absorptiometry (DEXA) scans demonstrated overall limb fat loss in stavudine treated patients compared to limb fat gain or no change in patients treated with other NRTIs (abacavir, tenofovir or zidovudine). The incidence and severity of lipoatrophy are cumulative over time with stavudine-containing regimens. In clinical trials, switching from stavudine to other nucleosides (tenofovir or abacavir) resulted in increases in limb fat with modest to no improvements in clinical lipoatrophy. Given the potential risks of using Zerit including lipoatrophy, a benefit-risk assessment for each patient should be made and an alternative antiretroviral carefully considered. Patients receiving Zerit should be frequently examined and questioned for signs of lipoatrophy. When such development is found, discontinuation of Zerit should be considered.

Weight and metabolic parameters: an increase in weight and in levels of blood lipids and glucose may occurr during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Peripheral neuropathy: up to 20% of patients treated with Zerit will develop peripheral neuropathy, often starting after some months of treatment. Patients with a history of neuropathy, or with other risk factors (for example alcohol, medicines such as isoniazid) are at particular risk. Patients should be monitored for symptoms (persistent numbness, tingling or pain in feet/hands) and if present patients should be switched to an alternate treatment regimen (see section 4.2 and Not recommended combinations, below).

Pancreatitis: patients with a history of pancreatitis had an incidence of approximately 5% on Zerit, as compared to approximately 2% in patients without such a history. Patients with a high risk of

pancreatitis or those receiving products known to be associated with pancreatitis should be closely followed for symptoms of this condition.

Immune reactivation syndrome: in HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis: although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Lactose intolerance: the hard capsule contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

Not recommended combinations: pancreatitis (fatal and nonfatal) and peripheral neuropathy (severe in some cases) have been reported in HIV infected patients receiving stavudine in association with hydroxyurea and didanosine (see section 4.3). Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV-infected patients treated with antiretroviral agents and hydroxyurea; fatal hepatic events were reported most often in patients treated with stavudine, hydroxyurea and didanosine. Hence hydroxyurea should not be used in the treatment of HIV infection.

Elderly: Zerit has not been specifically investigated in patients over the age of 65.

Paediatric population

Infants under the age of 3 months: safety data are available from clinical trials up to 6 weeks of treatment in 179 newborns and infants < 3 months of age (see section 4.8).
Special consideration should be given to the antiretroviral treatment history and the resistance profile of the HIV strain of the mother.

Mitochondrial dysfunction following exposure in utero: nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues (see also section 4.8); these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, that present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

4.5 Interaction with other medicinal products and other forms of interaction

The combination of stavudine with didanosine is contraindicated given that both drugs exhibits high risk of mitochondrial toxicity (see sections 4.3 and 4.4).

Since stavudine is actively secreted by the renal tubules, interactions with other actively secreted medicinal products are possible, e.g. with trimethoprim. No clinically relevant pharmacokinetic interaction has, however, been seen with lamivudine.

Zidovudine and stavudine are phosphorylated by the cellular enzyme (thymidine kinase), which preferentially phosphorylates zidovudine, thereby decreasing the phosphorylation of stavudine to its active triphosphate form. Zidovudine is therefore not recommended to be used in combination with stavudine.

In vitro studies indicate that the activation of stavudine is inhibited by doxorubicin and ribavirin but not by other medicinal products used in HIV infection which are similarly phosphorylated (e.g. didanosine, zalcitabine, ganciclovir and foscarnet) therefore, coadministration of stavudine with either doxorubicin or ribavirin should be undertaken with caution. Stavudine's influence on the phosphorylation kinetics of nucleoside analogues other than zidovudine has not been investigated.

Clinically significant interactions of stavudine or stavudine plus didanosine with nelfinavir have not been observed.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with medicines metabolised through these pathways.

Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound medicines.

There have been no formal interaction studies with other medicinal products.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Zerit should not be used during pregnancy unless clearly necessary.
Clinical experience in pregnant women is limited, but congenital anomalies and abortions have been reported.

In study AI455-094, performed in South-Africa, 362 mother-infant pairs were included in a prevention of mother-to-child-transmission study. Treatment naive pregnant women were enrolled into the study at gestation week 34-36 and given antiretroviral treatment until delivery. Antiretroviral prophylaxis, the same medications as given to the mother, was given to the new-born infant within 36 hours of delivery and continued for 6 weeks. In the stavudine containing arms, the neonates were treated for 6 weeks with stavudine 1 mg/kg BID. The follow-up time was up to 24 weeks of age.
The mother-infant pairs were randomised to receive either stavudine (N= 91), didanosine (N= 94), stavudine + didanosine (N= 88) or zidovudine (N= 89).
95% Confidence intervals for the mother-to-child-transmission rates were 5.4-19.3% (stavudine), 5.2-18.7% (didanosine); 1.3-11.2% (stavudine + didanosine); and 1.9-12.6% for zidovudine.

Preliminary safety data from this study (see also section 4.8), showed an increased infant mortality in the stavudine + didanosine (10%) treatment group compared to the stavudine (2%), didanosine (3%) or zidovudine (6%) groups, with a higher incidence of stillbirths in the stavudine + didanosine group. Data on lactic acid in serum were not collected in this study.

However lactic acidosis, sometimes fatal, has been reported in pregnant women who received the combination of didanosine and stavudine with or without other anti-retroviral treatment (see sections 4.3 and 4.4). Embryo-foetal toxicities were seen only at high exposure levels in animals. Preclinical studies showed placental transfer of stavudine (see section 5.3). Until additional data become available, Zerit should be given during pregnancy only after special consideration; there is insufficient information to recommend Zerit for prevention of mother-to-child transmission of HIV.

Breast-feeding

It is recommended that HIV infected women should not breast-feed under any circumstances in order to avoid transmission of HIV.
The data available on stavudine excretion into human breast milk are insufficient to assess the risk to the infant. Studies in lactating rats showed that stavudine is excreted in breast milk. Therefore, mothers should be instructed to discontinue breast-feeding prior to receiving Zerit.

Fertility

No evidence of impaired fertility was seen in rats at high exposure levels (up to 216 times that observed at the recommended clinical dose).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Stavudine may cause dizziness and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

Stavudine therapy is associated with several severe adverse reactions, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity. Given these potential risks, a benefit-risk assessment for each patient should be made and an alternative antiretroviral should be carefully considered (see section 4.4 and below).

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported in < 1% of patients taking stavudine in combination with other antiretrovirals (see section 4.4).

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including Zerit. Most of these cases occurred in the setting of symptomatic hyperlactatemia or lactic acidosis syndrome (see section 4.4). The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Hepatitis or liver failure, which was fatal in some cases, has been reported with the use of stavudine (see section 4.4).

Lipoatrophy was commonly reported in patients treated with stavudine in combination with other antiretrovirals (see section 4.4).

Peripheral neuropathy was seen in combination studies of Zerit with lamivudine plus efavirenz; the frequency of peripheral neurologic symptoms was 19% (6% for moderate to severe) with a rate of discontinuation due to neuropathy of 2%. The patients usually experienced resolution of symptoms after dose reduction or interruption of stavudine.

Pancreatitis, occasionally fatal, has been reported in up to 2-3% of patients enrolled in monotherapy clinical studies (see section 4.4). Pancreatitis was reported in < 1% of patients in combination therapy studies with Zerit.

Tabulated summary of adverse reactions

Adverse reactions of moderate or greater severity with at least a possible relationship to treatment regimen (based on investigator attribution) reported from 467 patients treated with Zerit in combination with lamivudine and efavirenz in two randomised clinical trials and along-term follow-up study (follow-up: median 56 weeks ranging up to 119 weeks) are listed below. Also listed are adverse reactions observed post-marketing in association with stavudine-containing antiretroviral treatment. The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders:	rare: anaemia* very rare: neutropenia *, thrombocytopenia*
Endocrine disorders:	uncommon: gynaecomastia
Metabolism and nutrition disorders:	common: lipoatrophy**, asymptomatic hyperlactatemia uncommon: lactic acidosis (in some cases involving motor weakness), anorexia rare: hyperglycaemia* very rare: diabetes mellitis*
Psychiatric disorders:	common: depression uncommon: anxiety, emotional lability
Nervous system disorders:	common: peripheral neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis; dizziness; abnormal dreams; headache; insomnia; abnormal thinking; somnolence very rare: motor weakness* (most often reported in the setting of symptomatic hyperlactatemia or lactic acidosis syndrome)
Gastrointestinal disorders:	common: diarrhoea, abdominal pain, nausea, dyspepsia uncommon: pancreatitis, vomiting
Hepatobiliary disorders:	uncommon: hepatitis or jaundice rare: hepatic steatosis very rare: liver failure*
Skin and subcutaneous tissue disorders:	common: rash, pruritus uncommon: urticaria
Musculoskeletal and connective tissue disorders:	uncommon: arthralgia, myalgia
General disorders and administration site conditions:	common: fatigue uncommon: asthenia

* Adverse reactions observed post-marketing in association with stavudine-containing antiretroviral treatment

** See Section Description of selected adverse reactions for more details.

Description of selected adverse reactions

Immune reactivation syndrome: in HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Lipoatrophy: stavudine has been shown to cause loss of subcutaneous fat, which is most evident in the face, limbs and buttocks. The incidence and severity of lipoatrophy are related to cumulative exposure, and is often not reversible when stavudine treatment is stopped. Patients receiving Zerit should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with Zerit should not be continued (see section 4.4).

Metabolic parameters: weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Osteonecrosis: cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Laboratory abnormalities: laboratory abnormalities reported in these two trials and an ongoing follow-up study included elevations of ALT (> 5 x ULN) in 3%, of AST (> 5 x ULN) in 3%, of lipase (≥ 2.1 ULN) in 3% of the patients in the Zerit group. Neutropenia (< 750 cells/mm^3) was reported in 5%, thrombocytopenia (platelets < 50,000/mm^3) in 2%, and low haemoglobin (< 8 g/dl) in < 1% of patients receiving Zerit.
Macrocytosis was not evaluated in these trials, but was found to be associated with Zerit in an earlier trial (MCV > 112 fl occurred in 30% of patients treated with Zerit).

Paediatric population

Adolescents, children and infants: adverse reactions and serious laboratory abnormalities reported to occur in paediatric patients ranging in age from birth through adolescence who received stavudine in clinical studies were generally similar in type and frequency to those seen in adults. However, clinically significant peripheral neuropathy is less frequent. These studies include ACTG 240, where 105 paediatric patients ages 3 months to 6 years received Zerit 2 mg/kg/day for a median of 6.4 months; a controlled clinical trial where 185 newborns received Zerit 1 mg/kg/day either alone or in combination with didanosine from birth through 6 weeks of age; and a clinical trial where 8 newborns received Zerit 2 mg/kg/day in combination with didanosine and nelfinavir from birth through 4 weeks of age.

In study AI455-094 (see also section 4.6), the safety follow-up period was restricted to only six months, which may be insufficient to capture long-term data on neurological adverse events and mitochondrial toxicity. Relevant grade 3-4 laboratory abnormalities in the 91 stavudine treated infants were low neutrophils in 7%, low hemoglobin in 1%, ALT increase in 1% and no lipase abnormality. Data on lactic acid in serum were not collected. No notable differences in the frequency of adverse drug reactions were seen between treatment groups. There was, however, an increased infant mortality in the stavudine + didanosine (10%) treatment group compared to the stavudine (2%), didanosine (3%) or zidovudine (6%) groups, with a higher incidence of stillbirths in the stavudine + didanosine group.

Mitochondrial dysfunction: review of the postmarketing safety database shows that adverse reactions indicative of mitochondrial dysfunction have been reported in the neonate and infant population exposed to one or more nucleoside analogues (see also section 4.4). The HIV status for the newborns and infants ≤ 3 months of age was negative, for older infants it tended to be positive. The profile of the adverse events for newborns and infants ≤ 3 months of age showed increases in lactic acid levels, neutropenia, anaemia, thrombocytopenia, hepatic transaminase increases and increased lipids, including hypertriglyceridaemia. The number of reports in older infants was too small to identify a pattern.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Experience in adults treated with up to 12 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage could include peripheral neuropathy and hepatic dysfunction. The mean haemodialysis clearance of stavudine is 120 ml/min. The contribution of this to the total elimination in an overdose situation is unknown. It is not known whether stavudine is removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF04

Mechanism of action

Stavudine, a thymidine analogue, is phosphorylated by cellular kinases to stavudine triphosphate which inhibits HIV reverse transcriptase by competing with the natural substrate, thymidine triphosphate. It also inhibits viral DNA synthesis by causing DNA chain termination due to lack of the 3'-hydroxyl group necessary for DNA elongation. Cellular DNA polymerase γ is also sensitive to inhibition by stavudine triphosphate, while cellular polymerases α and β are inhibited at concentrations 4,000-fold and 40-fold higher, respectively, than that needed to inhibit HIV reverse transcriptase.

Resistance

Stavudine treatment can select for and/or maintain thymidine analogue mutations (TAMs) associated with zidovudine resistance. The decrease of susceptibility *in vitro* is mutation requiring two or more TAMs (generally M41L and T215Y) before stavudine susceptibility is decreased (> 1.5 fold). These TAMs are seen at a similar frequency with stavudine and zidovudine in virological treatment. The clinical relevance of these findings suggest that stavudine should be generally avoided in the presence of TAMs, especially M41L and T215Y.
The activity of stavudine is also affected by multi-drug resistance associated mutations such as Q151M. In addition, K65R has been reported in patients receiving stavudine/didanosine or stavudine/lamivudine, but not in patients receiving stavudine monotherapy. V75T is selected *in vitro* by stavudine and reduces susceptibility to stavudine by 2-fold. It occurs in ~1% of patients receiving stavudine.

Clinical efficacy and safety

Zerit has been studied in combination with other antiretroviral agents, e.g. didanosine, lamivudine, ritonavir, indinavir, saquinavir, efavirenz, and nelfinavir.

In antiretroviral naive patients

Study AI455-099 was a 48-week, randomised, double-blind study with Zerit (40 mg twice daily), in combination with lamivudine (150 mg twice daily) plus efavirenz (600 mg once daily), in 391 treatment-naive patients, with a median CD4 cell count of 272 cells/mm^3 (range 61 to 1215 cells/mm^3) and a median plasma HIV-1 RNA of 4.80 log_{10} copies/ml (range 2.6 to 5.9 log_{10} copies/ml) at baseline. Patients were primarily males (70%) and non-white (58%) with a median age of 33 years (range 18 to 68 years).

Study AI455-096 was a 48-week, randomised, double-blind study with Zerit (40 mg twice daily), in combination with lamivudine (150 mg twice daily) plus efavirenz (600 mg once daily), in 76 treatment-naive patients, with a median CD4 cell count of 261 cells/mm^3 (range 63 to 962 cells/mm^3) and a median plasma HIV-1 RNA of 4.63 log_{10} copies/ml (range 3.0 to 5.9 log_{10} copies/ml) at baseline. Patients were primarily males (76%) and white (66%) with a median age of 34 years (range 22 to 67 years).

The results of AI455-099 and AI455-096 are presented in Table 1. Both studies were designed to compare two formulations of Zerit, one of which was the marketed formulation dosed as currently approved in product labelling. Only the data from the marketed formulation are presented.

Table 1: Efficacy Outcomes at Week 48 (Studies AI455-099 and AI455-096)

	AI455-099	**AI455-096**
Parameter	Zerit + lamivudine + efavirenz **n=391**	Zerit + lamivudine + efavirenz **n=76**
HIV RNA < 400 copies/ml, treatment response, %		
All patients	73	66
HIV RNA < 50 copies/ml, treatment response, %		
All patients	55	38
HIV RNA Mean Change from Baseline, log_{10} copies/ml		
All patients	-2.83 (n=321[a])	-2.64 (n=58)
CD4 Mean Change from Baseline, cells/mm^3		
All patients	182 (n=314)	195 (n=55)

[a] Number of patients evaluable.

Paediatric population

The use of stavudine in adolescents, children and infants is supported by pharmacokinetic and safety data in paediatric patients (see also sections 4.8 and 5.2).

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability is 86±18%. After multiple oral administration of 0.5-0.67 mg/kg doses, a C_{max} value of 810±175 ng/ml was obtained. C_{max} and AUC increased proportionally with dose in the dose ranges, intravenous 0.0625-0.75 mg/kg, and oral 0.033-4.0 mg/kg.
In eight patients receiving 40 mg twice daily in the fasted state, steady-state AUC_{0-12h} was 1284±227 ng·h/ml (18%) (mean ± SD [% CV]), C_{max} was 536±146 ng/ml (27%), and C_{min} was 9±8 ng/ml (89%). A study in asymptomatic patients demonstrated that systemic exposure is similar while C_{max} is lower and T_{max} is prolonged when stavudine is administered with a standardised, high-fat meal compared with fasting conditions. The clinical significance of this is unknown.

Distribution

The apparent volume of distribution at steady state is 46±21 l. It was not possible to detect stavudine in cerebrospinal fluid until at least 2 hours after oral administration. Four hours after administration, the CSF/plasma ratio was 0.39±0.06. No significant accumulation of stavudine is observed with repeated administration every 6, 8, or 12 hours.
Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 µg/ml. Stavudine distributes equally between red blood cells and plasma.

Metabolism

Unchanged stavudine was the major drug-related component in total plasma radioactivity circulating after an oral 80 mg dose of ^{14}C-stavudine in healthy subjects. The AUC(*inf*) for stavudine was 61% of the AUC(*inf*) of the total circulating radioactivity. Metabolites include oxidised stavudine, glucuronide conjugates of stavudine and its oxidised metabolite, and an *N*-acetylcysteine conjugate of the ribose after glycosidic cleavage, suggesting that thymine is also a metabolite of stavudine.

Elimination

Following an oral 80-mg dose of ^{14}C-stavudine to healthy subjects, approximately 95% and 3% of the total radioactivity was recovered in urine and faeces, respectively. Approximately 70% of the orally administered stavudine dose was excreted as an unchanged drug in urine. Mean renal clearance of the parent compound is approximately 272 ml/min, accounting for approximately 67% of the apparent oral clearance, indicating active tubular secretion in addition to glomerular filtration.

In HIV-infected patients,total clearance of stavudine is 594±164 ml/min, and renal clearance is 237±98 ml/min. The total clearance of stavudine appears to be higher in HIV-infected patients, while the renal clearance is similar between healthy subjects and HIV-infected patients. The mechanism and clinical significance of this difference are unknown. After intravenous administration, 42% (range: 13% to 87%) of dose is excreted unchanged in the urine. The corresponding values after oral single and multiple dose administration are 35% (range: 8% to 72%) and 40% (range: 12% to 82%), respectively. The mean terminal elimination half-life of stavudine is 1.3 to 2.3 hours following single or multiple doses, and is independent of dose. *In vitro*, stavudine triphosphate has an intracellular half-life of 3.5 hours in CEM T-cells (a human T-lymphoblastoid cell line) and peripheral blood mononuclear cells, supporting twice daily dosing.
The pharmacokinetics of stavudine was independent of time, since the ratio between $AUC_{(ss)}$ at steady state and the $AUC_{(0-t)}$ after the first dose was approximately 1. Intra- and inter-individual variation in pharmacokinetic characteristics of stavudine is low, approximately 15% and 25%, respectively, after oral administration.

Special Populations

Renal impairment: the clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of Zerit be adjusted in patients with reduced renal function (see section 4.2).

Hepatic impairment: stavudine pharmacokinetics in patients with hepatic impairment were similar to those in patients with normal hepatic function.

Paediatric population

Adolescents, children and infants: total exposure to stavudine was comparable between adolescents, children and infants ≥ 14 days receiving the 2 mg/kg/day dose and adults receiving 1 mg/kg/day. Apparent oral clearance was approximately 14 ml/min/kg for infants ages 5 weeks to 15 years, 12 ml/min/kg for infants ages 14 to 28 days, and 5 ml/min/kg for infants on the day of birth. Two to three hours post-dose, CSF/plasma ratios of stavudine ranged from 16% to 125% (mean of 59%±35%).

5.3 Preclinical safety data

Animal data showed embryo-foetal toxicity at very high exposure levels. An *ex vivo* study using a term human placenta model demonstrated that stavudine reaches the foetal circulation by simple diffusion. A rat study also showed placental transfer of stavudine, with the foetal tissue concentration approximately 50% of the maternal plasma concentration.
Stavudine was genotoxic in *in vitro* tests in human lymphocytes possessing triphosphorylating activity (in which no no-effect level was established), in mouse fibroblasts, and in an *in vivo* test for chromosomal aberrations. Similar effects have been observed with other nucleoside analogues.
Stavudine was carcinogenic in mice (liver tumours) and rats (liver tumours: cholangiocellular, hepatocellular, mixed hepatocholangiocellular, and/or vascular; and urinary bladder carcinomas) at very high exposure levels. No carcinogenicity was noted at doses of 400 mg/kg/day in mice and 600 mg/kg/day in rats, corresponding to exposures ~ 39 and 168 times the expected human exposure, respectively, suggesting an insignificant carcinogenic potential of stavudine in clinical therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose
Magnesium stearate
Microcrystalline cellulose
Sodium starch glycolate

Capsule shell
Gelatin
Iron oxide colorant (E172)
Silicon dioxide
Sodium laurilsulphate
Titanium dioxide (E171)

Black ink containing
Shellac
Propylene Glycol
Purified Water
Potassium Hydroxide
Iron Oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C (aclar/alu blisters).
Do not store above 30°C (HDPE bottles).
Store in the original package.

6.5 Nature and contents of container

HDPE bottles with child resistant screw cap (60 hard capsules per bottle).

Aclar/aluminium blisters with 14 hard capsules per card and 4 cards (56 hard capsules) per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254

Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/001 - 008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 May 1996
Date of last renewal: 20 April 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Zerit 200 mg powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 200 mg of stavudine.
The reconstituted solution contains 1 mg of stavudine per ml.

Excipients with known effect
Each bottle contains 31.5 mg of propylhydroxybenzoate (E216)
Each bottle contains 315 mg of methylhydroxybenzoate (E218)
Each bottle contains 10.15 g of sucrose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution.

Off-white to pale-pink, gritty powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zerit is indicated in combination with other antiretroviral medicinal products for the treatment of HIV infected adult patients and paediatric patients (from birth) only when other antiretrovirals can not be used. The duration of therapy with Zerit should be limited to the shortest time possible (see section 4.2).

4.2 Posology and method of administration

The therapy should be initiated by a doctor experienced in the management of HIV infection (see also section 4.4).

For patients starting therapy with Zerit, the duration should be limited to the shortest time possible followed by a switch to an alternative appropriate therapy whenever possible. Patients continuing treatment with Zerit should be assessed frequently and switched to an alternative appropriate therapy whenever possible (see section 4.4).

Posology

Adults: the recommended oral dosage is

Patient weight	Zerit dosage
< 60 kg	30 mg twice daily (every 12 hours)
≥ 60 kg	40 mg twice daily (every 12 hours)

Paediatric population

Adolescents, children and infants: the recommended oral dosage is

Patient age and/or weight	Zerit dosage
From birth* to 13 days old	0.5 mg/kg twice daily (every 12 hours)

At least 14 days old and < 30 kg	1 mg/kg twice daily (every 12 hours)
≥ 30 kg	adult dosing

*The reduced posology in neonates from 0 to 13 days is based on average study data and may not correspond to invidual variation in kidney maturation. Dosing recommendations are not available for neonates with a gestational age < 37 weeks.

The powder formulation of Zerit should be used for infants under the age of 3 months. Adult patients that have problems swallowing capsules should ask their doctor about the possibility of changing to the powder formulation of this medicine.

Instructions for preparation, see section 6.6.

Dose adjustments

Peripheral neuropathy: if symptoms of peripheral neuropathy develop (usually characterised by persistent numbness, tingling, or pain in the feet and/or hands) (see section 4.4), patients should be switched to an alternative treatment regimen, if appropriate. In the rare cases when this is inappropriate, dose reduction of stavudine may be considered, while the symptoms of peripheral neuropathy are under close monitoring and satisfactory virological suppression is maintained. The possible benefits of a dose reduction should be balanced in each case against the risks - which may result from this measure (lower intracellular concentrations).

Special populations

Elderly: Zerit has not been specifically investigated in patients over the age of 65.

Hepatic impairment: no initial dosage adjustment is necessary.

Renal impairment: the following dosages are recommended

Patient weight	Zerit dosage (according to creatinine clearance)	
	26-50 ml/min	≤ 25 ml/min (including dialysis dependence*)
< 60 kg	15 mg twice daily	15 mg every 24 hours
≥ 60 kg	20 mg twice daily	20 mg every 24 hours

* Patients on haemodialysis should take Zerit after the completion of haemodialysis, and at the same time on non-dialysis days.

Since urinary excretion is also a major route of elimination of stavudine in paediatric patients, the clearance of stavudine may be altered in paediatric patients with renal impairment. Although there are insufficient data to recommend a specific dosage adjustment of Zerit in this patient population, a reduction in the dose and/or an increase in the interval between doses proportional to the reduction for adults should be considered. There are no dosage recommendations for paediatric patients under the age of 3 months with renal impairment.

Method of administration

For optimal absorption, Zerit should be taken on an empty stomach (i.e. at least 1 hour prior to meals) but, if this is not possible, it may be taken with a light meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with didanosine due to the potential for serious and/or life-threatening events notably lactic acidosis, liver function abnormalities, pancreatitis and peripheral neuropathy (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Stavudine therapy is associated with several severe side effects, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity. Given these potential risks, a benefit-risk assessment for each patients should be made and an alternative antiretroviral should be carefully considered (see *Lactic acidosis*, *Lipoatrophy,* and *Peripheral neuropathy* below and section 4.8).

Lactic acidosis: lactic acidosis, usually associated with hepatomegaly and hepatic steatosis has been reported with the use of stavudine. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, renal failure, or motor paralysis.
Lactic acidosis generally occurred after a few or several months of treatment.
Treatment with stavudine should be discontinued if there is symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
Caution should be exercised when administering stavudine to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.
Patients at increased risk should be followed closely (see also section 4.6).

Liver disease: hepatitis or liver failure, which was fatal in some cases, has been reported. The safety and efficacy of stavudine has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

In the event of rapidly elevating transaminase levels (ALT/AST, > 5 times upper limit of normal, ULN), discontinuation of Zerit and any potentially hepatotoxic medicinal products should be considered.

Lipoatrophy: on the basis of mitochondrial toxicity stavudine has been shown to cause loss of subcutaneous fat, which is most evident in the face, limbs and buttocks.

In randomized controlled trials of treatment-naive patients, clinical lipoatrophy developed in a higher proportion of patients treated with stavudine compared to other nucleosides (tenofovir or abacavir). Dual energy x-ray absorptiometry (DEXA) scans demonstrated overall limb fat loss in stavudine treated patients compared to limb fat gain or no change in patients treated with other NRTIs (abacavir, tenofovir or zidovudine). The incidence and severity of lipoatrophy are cumulative over time with stavudine-containing regimens. In clinical trials, switching from stavudine to other nucleosides (tenofovir or abacavir) resulted in increases in limb fat with modest to no improvements in clinical

lipoatrophy. Given the potential risks of using Zerit including lipoatrophy, a benefit-risk assessment for each patient should be made and an alternative antiretroviral carefully considered. Patients receiving Zerit should be frequently examined and questioned for signs of lipoatrophy. When such development is found, discontinuation of Zerit should be considered.

Weight and metabolic parameters: an increase in weight and in levels of blood lipids and glucose may occurr during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Peripheral neuropathy: up to 20% of patients treated with Zerit will develop peripheral neuropathy, often starting after some months of treatment. Patients with a history of neuropathy, or with other risk factors (for example alcohol, medicines such as isoniazid) are at particular risk. Patients should be monitored for symptoms (persistent numbness, tingling or pain in feet/hands) and if present patients should be switched to an alternate treatment regimen (see section 4.2 and Not recommended combinations, below).

Pancreatitis: patients with a history of pancreatitis had an incidence of approximately 5% onZerit, as compared to approximately 2% in patients without such a history. Patients with a high risk of pancreatitis or those receiving products known to be associated with pancreatitis should be closely followed for symptoms of this condition.

Immune reactivation syndrome: in HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis: although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Excipients: the reconstituted powder for oral solution contains 50 mg sucrose per ml of reconstituted solution. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth.
This product contains methylhydroxybenzoate (E218) and propylhydroxybenzoate (E216) that may cause allergic reactions (possibly delayed).

Not recommended combinations: pancreatitis (fatal and nonfatal) and peripheral neuropathy (severe in some cases) have been reported in HIV infected patients receiving stavudine in association with hydroxyurea and didanosine (see section 4.3). Hepatotoxicity and hepatic failure resulting in death were reported during postmarketing surveillance in HIV infected patients treated with antiretroviral agents and hydroxyurea; fatal hepatic events were reported most often in patients treated with stavudine, hydroxyurea and didanosine. Hence, hydroxyurea should not be used in the treatment of HIV infection.

Elderly: Zerit has not been specifically investigated in patients over the age of 65.

Paediatric population

Infants under the age of 3 months: safety data are available from clinical trials up to 6 weeks of treatment in 179 newborns and infants < 3 months of age (see section 4.8).
Special consideration should be given to the antiretroviral treatment history and the resistance profile of the HIV strain of the mother.

Mitochondrial dysfunction following exposure in utero: nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues (see also section 4.8); these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, that present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

4.5 Interaction with other medicinal products and other forms of interaction

The combination of stavudine with didanosine is contraindicated given that both drugs exhibits high risk of mitochondrial toxicity (see sections 4.3 and 4.4).

Since stavudine is actively secreted by the renal tubules, interactions with other actively secreted medicinal products are possible, e.g. with trimethoprim. No clinically relevant pharmacokinetic interaction has, however, been seen with lamivudine.

Zidovudine and stavudine are phosphorylated by the cellular enzyme (thymidine kinase), which preferentially phosphorylates zidovudine, thereby decreasing the phosphorylation of stavudine to its active triphosphate form. Zidovudine is therefore not recommended to be used in combination with stavudine.

In vitro studies indicate that the activation of stavudine is inhibited by doxorubicin and ribavirin but not by other medicinal products used in HIV infection which are similarly phosphorylated, (e.g. didanosine, zalcitabine, ganciclovir and foscarnet) therefore, coadministration of stavudine with either doxorubicin or ribavirin should be undertaken with caution. Stavudine's influence on the phosphorylation kinetics of nucleoside analogues other than zidovudine has not been investigated.

Clinically significant interactions of stavudine or stavudine plus didanosine with nelfinavir have not been observed.

Stavudine does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with medicines metabolised through these pathways.

Because stavudine is not protein-bound, it is not expected to affect the pharmacokinetics of protein-bound medicines.

There have been no formal interaction studies with other medicinal products.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Zerit should not be used during pregnancy unless clearly necessary.
Clinical experience in pregnant women is limited, but congenital anomalies and abortions have been reported.

In study AI455-094, performed in South-Africa, 362 mother-infant pairs were included in a prevention of mother-to-child-transmission study. Treatment naive pregnant women were enrolled into the study at gestation week 34-36 and given antiretroviral treatment until delivery. Antiretroviral prophylaxis, the same medications as given to the mother, was given to the new-born infant within 36 hours of delivery and continued for 6 weeks. In the stavudine containing arms, the neonates were treated for 6 weeks with stavudine 1 mg/kg BID. The follow-up time was up to 24 weeks of age.
The mother-infant pairs were randomised to receive either stavudine (N= 91), didanosine (N= 94), stavudine + didanosine (N= 88) or zidovudine (N= 89).
95% Confidence intervals for the mother-to-child-transmission rates were 5.4-19.3% (stavudine), 5.2-18.7% (didanosine); 1.3-11.2% (stavudine + didanosine); and 4.9-12.6% for zidovudine.

Preliminary safety data from this study (see also section 4.8), showed an increased infant mortality in the stavudine + didanosine (10%) treatment group compared to the stavudine (2%), didanosine (3%) or zidovudine (6%) groups, with a higher incidence of stillbirths in the stavudine + didanosine group. Data on lactic acid in serum were not collected in this study.

However, lactic acidosis, sometimes fatal, has been reported in pregnant women who received the combination of didanosine and stavudine with or without other anti-retroviral treatment (see sections 4.3 and 4.4). Embryo-foetal toxicities were seen only at high exposure levels in animals. Preclinical studies showed placental transfer of stavudine (see section 5.3). Until additional data become available, Zerit should be given during pregnancy only after special consideration; there is insufficient information to recommend Zerit for prevention of mother-to-child transmission of HIV.

Breast-feeding

It is recommended that HIV infected women should not breast-feed under any circumstances in order to avoid transmission of HIV.
The data available on stavudine excretion into human breast milk are insufficient to assess the risk to the infant. Studies in lactating rats showed that stavudine is excreted in breast milk. Therefore, mothers should be instructed to discontinue breast-feeding prior to receiving Zerit.

Fertility

No evidence of impaired fertility was seen in rats at high exposure levels (up to 216 times that observed at the recommended clinical dose).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Stavudine may cause dizziness and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

Stavudine therapy is associated with several severe adverse reactions, such as lactic acidosis, lipoatrophy and polyneuropathy, for which a potential underlying mechanism is mitochondrial toxicity. Given these potential risks, a benefit-risk assessment for each patient should be made and an alternative antiretroviral should be carefully considered (see section 4.4 and below).

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported in < 1% of patients taking stavudine in combination with other antiretrovirals (see section 4.4).

Motor weakness has been reported rarely in patients receiving combination antiretroviral therapy including Zerit. Most of these cases occurred in the setting of symptomatic hyperlactatemia or lactic acidosis syndrome (see section 4.4). The evolution of motor weakness may mimic the clinical presentation of Guillain-Barré syndrome (including respiratory failure). Symptoms may continue or worsen following discontinuation of therapy.

Hepatitis or liver failure, which was fatal in some cases, has been reported with the use of stavudine (see section 4.4).

Lipoatrophy was commonly reported in patients treated with stavudine in combination with other antiretrovirals (see section 4.4).

Peripheral neuropathy was seen in combination studies of Zerit with lamivudine plus efavirenz; the frequency of peripheral neurologic symptoms was 19% (6% for moderate to severe) with a rate of discontinuation due to neuropathy of 2%. The patients usually experienced resolution of symptoms after dose reduction or interruption of stavudine.

Pancreatitis, occasionally fatal, has been reported in up to 2-3% of patients enrolled in monotherapy clinical studies (see section 4.4). Pancreatitis was reported in < 1% of patients in combination therapy studies with Zerit.

Tabulated summary of adverse reactions

Adverse reactions of moderate or greater severity with at least a possible relationship to treatment regimen (based on investigator attribution) reported from 467 patients treated with Zerit in combination with lamivudine and efavirenz in two randomised clinical trials and a long-term follow-up study (follow-up: median 56 weeks ranging up to 119 weeks) are listed below. Also listed are adverse reactions observed post-marketing in association with stavudine-containing antiretroviral treatment. The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders:	rare: anaemia* very rare: neutropenia*, thrombocytopenia*
Endocrine disorders:	uncommon: gynaecomastia
Metabolism and nutrition disorders:	common: lipoatrophy**, asymptomatic hyperlactatemia uncommon: lactic acidosis (in some cases involving motor weakness), anorexia rare: hyperglycaemia* very rare: diabetes mellitis*
Psychiatric disorders:	common: depression uncommon: anxiety, emotional lability

Nervous system disorders:	common: peripheral neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis; dizziness; abnormal dreams; headache, insomnia; abnormal thinking; somnolence very rare: motor weakness* (most often reported in the setting of symptomatic hyperlactatemia or lactic acidosis syndrome)
Gastrointestinal disorders:	common: diarrhoea, abdominal pain, nausea, dyspepsia uncommon: pancreatitis, vomiting
Hepatobiliary disorders:	uncommon: hepatitis or jaundice rare: hepatic steatosis* very rare: liver failure*
Skin and subcutaneous tissue disorders:	common: rash, pruritus uncommon: urticaria
Musculoskeletal and connective tissue disorders:	uncommon: arthralgia, myalgia
General disorders and administration site conditions:	common: fatigue uncommon: asthenia

* Adverse reactions observed post-marketing in association with stavudine-containing antiretroviral treatment

** See Section Description of selected adverse reactions for more details.

Description of selected adverse reactions

Immune reactivation syndrome: in HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Lipoatrophy: stavudine has been shown to cause loss of subcutaneous fat, which is most evident in the face, limbs and buttocks. The incidence and severity of lipoatrophy are related to cumulative exposure, and is often not reversible when stavudine treatment is stopped. Patients receiving Zerit should be frequently examined and questioned for signs of lipoatrophy. When such development is found, treatment with Zerit should not be continued (see section 4.4).

Metabolic parameters: weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Osteonecrosis: cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Laboratory abnormalities: laboratory abnormalities reported in these two trials and an ongoing follow-up study included elevations of ALT (> 5 x ULN) in 3%, of AST (> 5 x ULN) in 3%, of lipase (≥ 2.1 ULN) in 3% of the patients in the Zerit group. Neutropenia (< 750 cells/mm^3) was reported in 5%, thrombocytopenia (platelets < 50,000/mm^3) in 2%, and low haemoglobin (< 8 g/dl) in < 1% of patients receiving Zerit.
Macrocytosis was not evaluated in these trials, but was found to be associated with Zerit in an earlier trial (MCV > 112 fl occurred in 30% of patients treated with Zerit).

Paediatric population

Adolescents, children and infants: adverse reactions and serious laboratory abnormalities reported to occur in paediatric patients ranging in age from birth through adolescence who received stavudine in clinical studies were generally similar in type and frequency to those seen in adults. However, clinically significant peripheral neuropathy is less frequent. These studies include ACTG 240, where 105 paediatric patients ages 3 months to 6 years received Zerit 2 mg/kg/day for a median of 6.4 months; a controlled clinical trial where 185 newborns received Zerit 2 mg/kg/day either alone or in combination with didanosine from birth through 6 weeks of age; and a clinical trial where 8 newborns received Zerit 2 mg/kg/day in combination with didanosine and nelfinavir from birth through 4 weeks of age.

In study AI455-094 (see also section 4.6), the safety follow-up period was restricted to only six months, which may be insufficient to capture long-term data on neurological adverse events and mitochondrial toxicity. Relevant grade 3-4 laboratory abnormalities in the 91 stavudine treated infants were low neutrophils in 7%, low hemoglobin in 1%, ALT increase in 1% and no lipase abnormality. Data on lactic acid in serum were not collected. No notable differences in the frequency of adverse drug reactions were seen between treatment groups. There was, however, an increased infant mortality in the stavudine + didanosine (10%) treatment group compared to the stavudine (2%), didanosine (3%) or zidovudine (6%) groups, with a higher incidence of stillbirths in the stavudine + didanosine group.

Mitochondrial dysfunction: review of the postmarketing safety database shows that adverse reactions indicative of mitochondrial dysfunction have been reported in the neonate and infant population exposed to one or more nucleoside analogues (see also section 4.4). The HIV status for the newborns and infants ≤ 3 months of age was negative, for older infants it tended to be positive. The profile of the adverse events for newborns and infants ≤ 3 months of age showed increases in lactic acid levels, neutropenia, anaemia, thrombocytopenia, hepatic transaminases increases and increased lipids, including hypertriglyceridaemia. The number of reports in older infants was too small to identify a pattern.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Experience in adults treated with up to 12 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage could include peripheral neuropathy and hepatic dysfunction. The mean haemodialysis clearance of stavudine is 120 ml/min. The contribution of this to the total elimination in an overdose situation is unknown. It is not known whether stavudine is removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF04

Mechanism of action

Stavudine, a thymidine analogue, is phosphorylated by cellular kinases to stavudine triphosphate which inhibits HIV reverse transcriptase by competing with the natural substrate, thymidine triphosphate. It also inhibits viral DNA synthesis by causing DNA chain termination due to a lack of the 3'-hydroxyl group necessary for DNA elongation. Cellular DNA polymerase γ is also sensitive to inhibition by stavudine triphosphate, while cellular polymerases α and β are inhibited at concentrations 4,000-fold and 40-fold higher, respectively, than that needed to inhibit HIV reverse transcriptase.

Resistance

Stavudine treatment can select for and/or maintain thymidine analogue mutations (TAMs) associated with zidovudine resistance. The decrease of susceptibility *in vitro* is subtle during two or more TAMs (generally M41L and T215Y) before stavudine susceptibility is decreased (>1.5 fold). These TAMs are seen at a similar frequency with stavudine and zidovudine in virological treatment. The clinical relevance of these findings suggest that stavudine should be generally avoided in the presence of TAMs, especially M41L and T215Y.
The activity of stavudine is also affected by multi-drug resistance associated mutations such as Q151M. In addition, K65R has been reported in patients receiving stavudine/didanosine or stavudine/lamivudine, but not in patients receiving stavudine monotherapy. V75T is selected *in vitro* by stavudine and reduces susceptibility to stavudine by 2 fold. It occurs in ~1% of patients receiving stavudine.

Clinical efficacy and safety

Zerit has been studied in combination with other antiretroviral agents, e.g. didanosine, lamivudine, ritonavir, indinavir, saquinavir, efavirenz, and nelfinavir.

In antiretroviral naive patients

Study AI455-099 was a 48-week, randomised, double-blind study withZerit (40 mg twice daily), in combination with lamivudine (150 mg twice daily) plus efavirenz (600 mg once daily), in 391 treatment-naive patients, with a median CD4 cell count of 272 cells/mm^3 (range 61 to 1215 cells/mm^3) and a median plasma HIV-1 RNA of 4.80 log_{10} copies/ml (range 2.6 to 6.9 log_{10} copies/ml) at baseline. Patients were primarily males (70%) and non-white (58%) with a median age of 33 years (range 18 to 68 years).

Study AI455-096 was a 48-week, randomised, double-blind study with Zerit (40 mg twice daily), in combination with lamivudine (150 mg twice daily) plus efavirenz (600 mg once daily), in 376 treatment-naive patients, with a median CD4 cell count of 261 cells/mm^3 (range 63 to 962 cells/mm^3) and a median plasma HIV-1 RNA of 4.63 log_{10} copies/ml (range 3.0 to 5.9 log_{10} copies/ml) at baseline. Patients were primarily males (76%) and white (66%) with a median age of 34 years (range 22 to 67 years).

The results of AI455-099 and AI455-096 are presented in Table 1. Both studies were designed to compare two formulations of Zerit, one of which was the marketed formulation dosed as currently approved in product labelling. Only the data from the marketed formulation are presented.

Table 1: Efficacy Outcomes at Week 48 (Studies AI455-099 and AI455-096)

	AI455-099	AI455-096
Parameter	Zerit + lamivudine + efavirenz **n=391**	Zerit + lamivudine + efavirenz **n=76**
HIV RNA < 400 copies/ml, treatment response, %		
All patients	73	66
HIV RNA < 50 copies/ml, treatment response, %		
All patients	55	38
HIV RNA Mean Change from Baseline, log_{10} copies/ml		
All patients	-2.83 (n=321[a])	-2.64 (n=58)
CD4 Mean Change from Baseline, cells/mm^3		
All patients	182 (n=314)	195 (n=55)

[a] Number of patients evaluable.

Paediatric population

The use of stavudine in adolescents, children and infants is supported by pharmacokinetic and safety data in paediatric patients (see also sections 4.8 and 5.2).

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability is 86±18%. After multiple oral administration of 0.5-0.67 mg/kg doses, a C_{max} value of 810±175 ng/ml was obtained. C_{max} and AUC increased proportionally with dose in the dose ranges, intravenous 0.0625-0.75 mg/kg, and oral 0.033-4.0 mg/kg.
In eight patients receiving 40 mg twice daily in the fasted state, steady-state AUC_{0-12h} was 1284±227 ng·h/ml (18%) (mean ± SD [% CV]), C_{max} was 536±146 ng/ml (27%), and C_{min} was 9±8 ng/ml (89%). A study in asymptomatic patients demonstrated that systemic exposure is similar while C_{max} is lower and T_{max} is prolonged when stavudine is administered with a standardised, high-fat meal compared with fasting conditions. The clinical significance of this is unknown.

Distribution

The apparent volume of distribution at steady state is 46±21 l. It was not possible to detect stavudine in cerebrospinal fluid until at least 2 hours after oral administration. Four hours after administration, the CSF/plasma ratio was 0.39±0.06. No significant accumulation of stavudine is observed with repeated administration every 6, 8, or 12 hours.
Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 10.4 µg/ml. Stavudine distributes equally between red blood cells and plasma.

Metabolism

Unchanged stavudine was the major drug-related component in total plasma radioactivity circulating after an oral 80 mg dose of ^{14}C-stavudine in healthy subjects. The AUC(*inf*) for stavudine was 61% of the AUC(*inf*) of the total circulating radioactivity. Metabolites include oxidised stavudine, glucuronide conjugates of stavudine and its oxidised metabolite, and an *N*-acetylcysteine conjugate of the ribose after glycosidic cleavage, suggesting that thymine is also a metabolite of stavudine.

Elimination

Following an oral 80-mg dose of ^{14}C-stavudine to healthy subjects, approximately 95% and 3% of the total radioactivity was recovered in urine and faeces, respectively. Approximately 70% of the orally

administered stavudine dose was excreted as an unchanged drug in urine. Mean renal clearance of the parent compound is approximately 272 ml/min, accounting for approximately 67% of the apparent oral clearance, indicating active tubular secretion in addition to glomerular filtration.

In HIV-infected patients, total clearance of stavudine is 594±164 ml/min, and renal clearance is 237±98 ml/min. The total clearance of stavudine appears to be higher in HIV-infected patients, while the renal clearance is similar between healthy subjects and HIV-infected patients. The mechanism and clinical significance of this difference are unknown. After intravenous administration, 42% (range: 13% to 87%) of dose is excreted unchanged in the urine. The corresponding values after oral single and multiple dose administration are 35% (range: 8% to 72%) and 40% (range: 12% to 82%), respectively. The mean terminal elimination half-life of stavudine is 1.3 to 2.3 hours following single or multiple doses, and is independent of dose. *In vitro*, stavudine triphosphate has an intracellular half-life of 3.5 hours in CEM T-cells (a human T-lymphoblastoid cell line) and peripheral blood mononuclear cells, supporting twice daily dosing.
The pharmacokinetics of stavudine was independent of time, since the ratio between $AUC_{(ss)}$ at steady state and the $AUC_{(0-t)}$ after the first dose was approximately 1. Intra-and interindividual variation in pharmacokinetic characteristics of stavudine is low, approximately 15% and 25%, respectively, after oral administration.

Special Populations

Renal impairment: the clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of Zerit be adjusted in patients with reduced renal function (see section 4.2).

Hepatic impairment: stavudine pharmacokinetics in patients with hepatic impairment were similar to those in patients with normal hepatic function.

Paediatric population

Adolescents, children and infants: total exposure to stavudine was comparable between adolescents, children and infants ≥ 14 days receiving the 2 mg/kg/day dose and adults receiving 1 mg/kg/day. Apparent oral clearance was approximately 14 ml/min/kg for infants ages 5 weeks to 15 years, 12 ml/min/kg for infants ages 14 to 28 days, and 5 ml/min/kg for infants on the day of birth. Two to three hours post-dose CSF/plasma ratios of stavudine ranged from 16% to 125% (mean of 59%±35%).

5.3 Preclinical safety data

Animal data showed embryo-foetal toxicity at very high exposure levels. An *ex vivo* study using a term human placenta model demonstrated that stavudine reaches the foetal circulation by simple diffusion. A rat study also showed placental transfer of stavudine, with the foetal tissue concentration approximately 50% of the maternal plasma concentration.
Stavudine was genotoxic in *in vitro* tests in human lymphocytes possessing triphosphorylating activity (in which no no-effect level was established), in mouse fibroblasts, and in an *in vivo* test for chromosomal aberrations. Similar effects have been observed with other nucleoside analogues.
Stavudine was carcinogenic in mice (liver tumours) and rats (liver tumours: cholangiocellular, hepatocellular, mixed hepatocholangiocellular, and/or vascular; and urinary bladder carcinomas) at very high exposure levels. No carcinogenicity was noted at doses of 400 mg/kg/day in mice and 600 mg/kg/day in rats, corresponding to exposures ~ 39 and 168 times the expected human exposure, respectively, suggesting an insignificant carcinogenic potential of stavudine in clinical therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cherry flavour
Methylhydroxybenzoate (E218)
Propylhydroxybenzoate (E216)
Silicon dioxide
Simethicone
Sodium carmellose
Sorbic acid
Stearate emulsifiers
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After reconstitution, store the prepared oral solution in a refrigerator (2°C - 8°C) for 30 days.

6.4 Special precautions for storage

Do not store the dry powder above 30°C.
Store in the original package.
Keep the bottle tightly closed in order to protect from excessive moisture.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

HDPE bottle with child resistant screw cap, fill mark (200 ml of solution after reconstitution) and measuring cup.

6.6 Special precautions for disposal and other handling

Instructions for preparation

Zerit should be reconstituted with water to a 200 ml deliverable volume solution (stavudine concentration of 1 mg/ml).
To reconsistute Zerit, add 202 ml of water to the original bottle (when the patient makes up the solution, they should be instructed to fill to the top edge of the bottle label, indicated by the arrow marks). Replace the cap.
The bottle should be shaken well, until the powder dissolves completely. The solution appears as a colourless to slightly pink, hazy solution.
The solution should be dispensed with the measuring cup provided, or for doses less than 10 ml, dispense with a syringe. The patient should be instructed to shake the bottle well prior to measuring each dose.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 May 1996
Date of last renewal: 20 April 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Bristol-Myers Squibb S.r.l., Contrada Fontana del Ceraso, 03012 Anagni (FR), Italy

Aesica Queenborough Limited, North Road, Queenborough, Kent, ME11 5EL, United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 15 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 15 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zerit 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

Zerit 15 mg hard capsules
Stavudine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT AND BOTTLE LABEL TEXT (BOTTLE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 15 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 15 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
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Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: Zerit 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 20 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 20 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
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Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zerit 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
<NN:>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

Zerit 20 mg hard capsules
Stavudine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT AND BOTTLE LABEL TEXT (BOTTLE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 20 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 20 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
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Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: Zerit 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 30 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 30 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zerit 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
<NN:>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

Zerit 30 mg hard capsules
Stavudine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT AND BOTTLE LABEL TEXT (BOTTLE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 30 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 30 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: Zerit 30 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 40 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 40 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zerit 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
<NN:>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

Zerit 40 mg hard capsules
Stavudine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

BRISTOL-MYERS SQUIBB PHARMA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT AND BOTTLE LABEL TEXT (BOTTLE PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

Zerit 40 mg hard capsules
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 40 mg stavudine.

3. LIST OF EXCIPIENTS

Lactose

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: Zerit 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON TEXT AND BOTTLE LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT

Zerit 200 mg powder for oral solution
Stavudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each bottle contains stavudine 200 mg
The reconstituted solution contains 1 mg of stavudine per ml.

3. LIST OF EXCIPIENTS

Sucrose and preservatives (E218 and E216)

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution, 200 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Shake well before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Stable for 30 days after reconstitution, when stored in a refrigerator.
Store in the original package in order to protect from excessive moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/009/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: Zerit 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Outer carton: 2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Outer carton
PC:
SN:
<NN:>

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zerit 15 mg hard capsules
Stavudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zerit is and what it is used for

Zerit belongs to a particular group of antiviral medicines, also known as antiretrovirals, called nucleoside reverse transcriptase inhibitors (NRTIs).

These are used to treat Human Immunodeficiency Virus (HIV) infection.

This medicinal product, in combination with other antiretrovirals, reduces the HIV viral load and keeps it at a low level. It also increases CD4 cell counts. These CD4 cells play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Zerit varies between patients. Your doctor will therefore be monitoring the effectiveness of your treatment.

Zerit may improve your condition, but it is not a cure for your HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.
During treatment, other infections linked to a weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. What you need to know before you take Zerit

Do not take Zerit
- If you are allergic to stavudine or any of the other ingredients of this medicine (listed in section 6). Contact your doctor or pharmacist for advice.
  If you are taking didanosine, used to treat HIV infection.

Warnings and precautions
Talk to your doctor before taking Zerit.
Before treatment with Zerit, you should have told your doctor:
- if you suffer from kidney disease or liver disease (such as hepatitis)
- if you have had peripheral neuropathy (persistent numbness, tingling, or pain in the feet and/or hands)
- if you have suffered from pancreatitis (inflammation of the pancreas).

Zerit can cause a sometimes fatal condition called lactic acidosis, together with an enlarged liver. This condition usually does not occur until a few months after onset of treatment. This rare, but very serious side effect occurs more often in women, particularly if very overweight. In addition, rare cases of liver failure/renal failure or fatal hepatitis have been reported.
Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver side effects and may require blood tests for control of liver function.

If you develop one of the following, contact your doctor:
- persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), muscular weakness
- abdominal pain, nausea or vomiting
- rapid deep breathing, drowsiness (which may indicate pancreatitis, liver disturbance such as hepatitis, or lactic acidosis).

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

During therapy with Zerit there is often a gradual loss of subcutaneous fat (fat found beneath the skin), which is most notable in the face and on the legs and arms. Contact your doctor if you notice such changes.

Bone problems
Some patients taking Zerit may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pain (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Other medicines and Zerit
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Zerit if you are taking didanosine, used to treat HIV infection.

Tell your doctor if you are taking any of the following medicines, as undesirable interactions may occur:
- zidovudine, used to treat HIV infection
  doxorubicin, used to treat cancer
  ribavirin, used to treat hepatitis C infection.

Zerit with food and drink
For maximum effect, Zerit should be taken on an empty stomach, and preferably at least one hour before a meal. If this is not possible, the capsules may also be taken with a light meal.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
You must contact your doctor to discuss the potential side effects and the benefits and risks of your antiretroviral therapy to you and your child. Lactic acidosis (sometimes fatal) has been reported in pregnant women who received Zerit in combination with other antiretroviral treatment.
If you have taken Zerit during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding
Tell your doctor if you are breast-feeding. It is recommended that HIV-infected women should not breast-feed under any circumstances in order to avoid transmission of HIV to the baby.

Driving and using machines
Zerit may cause dizziness and drowsiness.
If you are affected, do not drive and do not use any tools or machines.

Zerit contains lactose
These capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Zerit

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely as they will give you the best chance to delay development of a resistance to the medicinal product. Do not change the dose on your own. Continue to take this medicine until your doctor tells you otherwise.
For adults whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
To obtain optimal absorption, the capsules should be swallowed with a glass of water, preferentially at least one hour before a meal and on an empty stomach. If this is not possible, Zerit may also be taken with a light meal.
If you have problems swallowing capsules you should ask your doctor about the possibility of changing to the solution form of this medicine or you could carefully open the capsule and mix its contents with some food.

Use in children
For children whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
Children older than 3 months, whose body weight is less than 30 kg, should receive 1 mg/kg twice daily.

If you take more Zerit than you should
If you have taken too many capsules or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor or the nearest hospital for advice.

If you forget to take Zerit
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zerit
The decision to stop using Zerit should be discussed with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zerit, or those caused by any other medicines you may be taking at the same time, or by the complications of the infection. For this reason, it is important that you inform your doctor of any change in your health.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Treatment with stavudine (Zerit) often causes a loss of fat from legs, arms and face (lipoatrophy). This loss of body fat has been shown to be not fully reversible after discontinuation of stavudine. Your doctor should monitor for signs of lipoatrophy. Tell your doctor if you notice any loss of fat from your legs, arms, and face. When these signs occur, Zerit should be stopped and your HIV treatment changed.

Patients treated with Zerit have reported the following side effects:

Common (may affect up to 1 in 10 people)
- asymptomatic hyperlactatemia (build up of acid in your blood)
- lipoatrophy
- depression
- peripheral neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis (numbness, weakness, tingling or pain in the arms and legs)
- dizziness, abnormal dreams, headache
- insomnia (difficulty sleeping), somnolence (sleepiness), abnormal thinking
- diarrhoea, abdominal pain (stomach pain or discomfort)
- nausea, dyspepsia (indigestion)
- rash, pruritus (itching)
- fatigue (extreme tiredness)

Uncommon (may affect up to 1 in 100 people)
- lactic acidosis (build up of acid in your blood) in some cases involving motor weakness (weakness in your arms, legs or hands)
- gynaecomastia (breast enlargement in men)
- anorexia (loss of appetite), anxiety, emotional lability
- pancreatitis (inflammation of the pancreas), vomiting
- hepatitis (inflammation of the liver), jaundice (yellow of the skin or eyes)
- urticaria (itchy rash), arthralgia (joint pain)
- myalgia (aching muscles), asthenia (unusual tiredness or weakness)

Rare (may affect up to 1 in 1,000 people)
- anemia
- hyperglycaemia (high sugar levels in the blood)
- hepatic steatosis (fat in the liver)

Very rare (may affect up to 1 in 10,000 people)
- thrombocytopenia, neutropenia (blood disorders)
- diabetes mellitus
- motor weakness (most often reported in the setting of symptomatic hyperlacetatemia or lactic acidosis syndrome)
- liver failure

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zerit

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the bottle label and/or the blister after EXP. The expiry date refers to the last day of that month.

Store below 25°C (aclar/alu blisters).
Do not store above 30°C (HDPE bottles).
Store in the original package.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zerit contains
- The active substance is stavudine (15 mg).
- The other ingredients of the powder contained in the hard capsule are: lactose (120 mg), magnesium stearate, microcrystalline cellulose and sodium starch glycolate.
- The ingredients of the capsule shell are gelatine, iron oxide colorant (E172), silicon dioxide, sodium laurilsulphate and titanium dioxide colorant (E171).
- The capsule shells are marked using edible black printing ink containing shellac, propylene glycol, purified water, potassium hydroxide and iron oxide (E172).

What Zerit looks like and content of the pack
Zerit 15 mg hard capsules are red and yellow and marked with “BMS 1964” on one side and “15” on the other side.
Zerit 15 mg hard capsules are supplied in blister packs of 56 hard capsules or bottles of 60 hard capsules. To help protect the capsules from excessive moisture, the bottle includes a desiccant canister.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
03012 Anagni (FR)
Italy

Aesica Queenborough Limited
North Road, Queenborough
Kent, ME11 5EL
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Tel: + 44 (0800) 731 1736

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

Zerit 20 mg hard capsules
Stavudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zerit is and what it is used for

Zerit belongs to a particular group of antiviral medicines, also known as antiretrovirals, called nucleoside reverse transcriptase inhibitors (NRTIs).

These are used to treat Human Immunodeficiency Virus (HIV) infection.

This medicinal product, in combination with other antiretrovirals, reduces the HIV viral load and keeps it at a low level. It also increases CD4 cell counts. These CD4 cells play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Zerit varies between patients. Your doctor will therefore be monitoring the effectiveness of your treatment.

Zerit may improve your condition, but it is not a cure for your HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.
During treatment, other infections linked to a weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. What you need to know before you take Zerit

Do not take Zerit
- If you are allergic to stavudine or any of the other ingredients of this medicine (listed in section 6). Contact your doctor or pharmacist for advice.
  If you are taking didanosine, used to treat HIV infection.

Warnings and precautions
Talk to your doctor before taking Zerit.
Before treatment with Zerit, you should have told your doctor:
- if you suffer from kidney disease or liver disease (such as hepatitis)
- if you have had peripheral neuropathy (persistent numbness, tingling, or pain in the feet and/or hands)
- if you have suffered from pancreatitis (inflammation of the pancreas).

Zerit can cause a sometimes fatal condition called lactic acidosis, together with an enlarged liver. This condition usually does not occur until a few months after onset of treatment. This rare, but very serious side effect occurs more often in women, particularly if very overweight. In addition, rare cases of liver failure/renal failure or fatal hepatitis have been reported.
Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver side effects and may require blood tests for control of liver function.

If you develop one of the following, contact your doctor:
- persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), muscular weakness
- abdominal pain, nausea or vomiting
- rapid deep breathing, drowsiness (which may indicate pancreatitis, liver disturbance such as hepatitis, or lactic acidosis).

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

During therapy with Zerit there is often a gradual loss of subcutaneous fat (fat found beneath the skin), which is most notable in the face and on the legs and arms. Contact your doctor if you notice such changes.

Bone problems
Some patients taking Zerit may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pain (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Other medicines and Zerit
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Zerit if you are taking didanosine, used to treat HIV infection.

Tell your doctor if you are taking any of the following medicines, as undesirable interactions may occur:
- zidovudine, used to treat HIV infection
- doxorubicin, used to treat cancer
- ribavirin, used to treat hepatitis C infection

Zerit with food and drink
For maximum effect, Zerit should be taken on an empty stomach, and preferably at least one hour before a meal. If this is not possible, the capsules may also be taken with a light meal.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
You must contact your doctor to discuss the potential side effects and the benefits and risks of your antiretroviral therapy to you and your child. Lactic acidosis (sometimes fatal) has been reported in pregnant women who received Zerit in combination with other antiretroviral treatment.
If you have taken Zerit during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding
Tell your doctor if you are breast-feeding. It is recommended that HIV-infected women should not breast-feed under any circumstances in order to avoid transmission of HIV to the baby.

Driving and using machines
Zerit may cause dizziness and drowsiness.
If you are affected, do not drive and do not use any tools or machines.

Zerit contains lactose
These capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Zerit

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely as they will give you the best chance to delay development of a resistance to the medicinal product. Do not change the dose on your own. Continue to take this medicine until your doctor tells you otherwise.
For adults whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
To obtain optimal absorption, the capsules should be swallowed with a glass of water, preferentially at least one hour before a meal and on an empty stomach. If this is not possible, Zerit may also be taken with a light meal.
If you have problems swallowing capsules you should ask your doctor about the possibility of changing to the solution form of this medicine or you could carefully open the capsule and mix its contents with some food.

Use in children
For children whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
Children older than 3 months, whose body weight is less than 30 kg, should receive 1 mg/kg twice daily.

If you take more Zerit than you should
If you have taken too many capsules or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor or the nearest hospital for advice.

If you forget to take Zerit
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zerit
The decision to stop using Zerit should be discussed with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zerit, or those caused by any other medicines you may be taking at the same time, or by the complications of the infection. For this reason, it is important that you inform your doctor of any change in your health.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Treatment with stavudine (Zerit) often causes a loss of fat from legs, arms and face (lipoatrophy). This loss of body fat has been shown to be not fully reversible after discontinuation of stavudine. Your doctor should monitor for signs of lipoatrophy. Tell your doctor if you notice any loss of fat from your legs, arms, and face. When these signs occur, Zerit should be stopped and your HIV treatment changed.

Patients treated with Zerit have reported the following side effects:

Common (may affect up to 1 in 10 people)
- asymptomatic hyperlactatemia (build up of acid in your blood)
- lipoatrophy
- depression
- peripheral neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis (numbness, weakness, tingling or pain in the arms and legs)
- dizziness, abnormal dreams, headache
- insomnia (difficulty sleeping), somnolence (sleepiness), abnormal thinking
- diarrhoea, abdominal pain (stomach pain or discomfort)
- nausea, dyspepsia (indigestion)
- rash, pruritus (itching)
- fatigue (extreme tiredness)

Uncommon (may affect up to 1 in 100 people)
- lactic acidosis (build up of acid in your blood) in some cases involving motor weakness (weakness in your arms, legs or hands)
- gynaecomastia (breast enlargement in men)
- anorexia (loss of appetite), anxiety, emotional lability
- pancreatitis (inflammation of the pancreas), vomiting
- hepatitis (inflammation of the liver), jaundice (yellow of the skin or eyes)
- urticaria (itchy rash), arthralgia (joint pain)
- myalgia (aching muscles), asthenia (unusual tiredness or weakness)

Rare (may affect up to 1 in 1,000 people)
- anemia
- hyperglycaemia (high sugar levels in the blood)
- hepatic steatosis (fat in the liver)

Very rare (may affect up to 1 in 10,000 people)
- thrombocytopenia, neutropenia (blood disorders)
- diabetes mellitus
- motor weakness (most often reported in the setting of symptomatic hyperlacetatemia or lactic acidosis syndrome)
- liver failure

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zerit

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the bottle label and/or the blister after EXP. The expiry date refers to the last day of that month.

Store below 25°C (aclar/alu blisters).
Do not store above 30°C (HDPE bottles).
Store in the original package.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zerit contains
- The active substance is stavudine (20 mg).
- The other ingredients of the powder contained in the hard capsule are: lactose (180 mg), magnesium stearate, microcrystalline cellulose and sodium starch glycolate.
- The ingredients of the capsule shell are gelatine, iron oxide colorant (E172), silicon dioxide, sodium laurilsulphate and titanium dioxide colorant (E171).
- The capsule shells are marked using edible black printing ink containing shellac, propylene glycol, purified water, potassium hydroxide and iron oxide (E172).

What Zerit looks like and content of the pack
Zerit 20 mg hard capsules are brown and marked with “BMS 1965” on one side and “20” on the other side.
Zerit 20 mg hard capsules are supplied in blister packs of 56 hard capsules or bottles of 60 hard capsules. To help protect the capsules from excessive moisture, the bottle includes a desiccant canister.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
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Italy

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

Zerit 30 mg hard capsules
Stavudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zerit is and what it is used for

Zerit belongs to a particular group of antiviral medicines, also known as antiretrovirals, called nucleoside reverse transcriptase inhibitors (NRTIs).

These are used to treat Human Immunodeficiency Virus (HIV) infection.

This medicinal product, in combination with other antiretrovirals, reduces the HIV viral load and keeps it at a low level. It also increases CD4 cell counts. These CD4 cells play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Zerit varies between patients. Your doctor will therefore be monitoring the effectiveness of your treatment.

Zerit may improve your condition, but it is not a cure for your HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.
During treatment, other infections linked to a weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. What you need to know before you take Zerit

Do not take Zerit
- If you are allergic to stavudine or any of the other ingredients of this medicine (listed in section 6). Contact your doctor or pharmacist for advice.
  If you are taking didanosine, used to treat HIV infection.

Warnings and precautions
Talk to your doctor before taking Zerit.
Before treatment with Zerit, you should have told your doctor:
- if you suffer from kidney disease or liver disease (such as hepatitis)
- if you have had peripheral neuropathy (persistent numbness, tingling, or pain in the feet and/or hands)
- if you have suffered from pancreatitis (inflammation of the pancreas).

Zerit can cause a sometimes fatal condition called lactic acidosis, together with an enlarged liver. This condition usually does not occur until a few months after onset of treatment. This rare, but very serious side effect occurs more often in women, particularly if very overweight. In addition, rare cases of liver failure/renal failure or fatal hepatitis have been reported.
Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver side effects and may require blood tests for control of liver function.

If you develop one of the following, contact your doctor:
- persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), muscular weakness
- abdominal pain, nausea or vomiting
- rapid deep breathing, drowsiness (which may indicate pancreatitis, liver disturbance such as hepatitis, or lactic acidosis).

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

During therapy with Zerit there is often a gradual loss of subcutaneous fat (fat found beneath the skin), which is most notable in the face and on the legs and arms. Contact your doctor if you notice such changes.

Bone problems
Some patients taking Zerit may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pain (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Other medicines and Zerit
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Zerit if you are taking didanosine, used to treat HIV infection.

Tell your doctor if you are taking any of the following medicines, as undesirable interactions may occur:
- zidovudine, used to treat HIV infection
- doxorubicin, used to treat cancer
- ribavirin, used to treat hepatitis C infection.

Zerit with food and drink
For maximum effect, Zerit should be taken on an empty stomach, and preferably at least one hour before a meal. If this is not possible, the capsules may also be taken with a light meal.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
You must contact your doctor to discuss the potential side effects and the benefits and risks of your antiretroviral therapy to you and your child. Lactic acidosis (sometimes fatal) has been reported in pregnant women who received Zerit in combination with other antiretroviral treatment.
If you have taken Zerit during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding
Tell your doctor if you are breast-feeding. It is recommended that HIV-infected women should not breast-feed under any circumstances in order to avoid transmission of HIV to the baby.

Driving and using machines
Zerit may cause dizziness and drowsiness.
If you are affected, do not drive and do not use any tools or machines.

Zerit contains lactose
These capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Zerit

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely as they will give you the best chance to delay development of a resistance to the medicinal product. Do not change the dose on your own. Continue to take this medicine until your doctor tells you otherwise.
For adults whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
To obtain optimal absorption, the capsules should be swallowed with a glass of water, preferentially at least one hour before a meal and on an empty stomach. If this is not possible, Zerit may also be taken with a light meal.
If you have problems swallowing capsules you should ask your doctor about the possibility of changing to the solution form of this medicine or you could carefully open the capsule and mix its contents with some food.

Use in children
For children whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
Children older than 3 months, whose body weight is less than 30 kg, should receive 1 mg/kg twice daily.

If you take more Zerit than you should
If you have taken too many capsules or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor or the nearest hospital for advice.

If you forget to take Zerit
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zerit
The decision to stop using Zerit should be discussed with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zerit, or those caused by any other medicines you may be taking at the same time, or by the complications of the infection. For this reason, it is important that you inform your doctor of any change in your health.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Treatment with stavudine (Zerit) often causes a loss of fat from legs, arms and face (lipoatrophy). This loss of body fat has been shown to be not fully reversible after discontinuation of stavudine. Your doctor should monitor for signs of lipoatrophy. Tell your doctor if you notice any loss of fat from your legs, arms, and face. When these signs occur, Zerit should be stopped and your HIV treatment changed.

Patients treated with Zerit have reported the following side effects:

Common (may affect up to 1 in 10 people)
- asymptomatic hyperlactatemia (build up of acid in your blood)
- lipoatrophy
- depression
- peripheral neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis (numbness, weakness, tingling or pain in the arms and legs)
- dizziness, abnormal dreams, headache
- insomnia (difficulty sleeping), somnolence (sleepiness), abnormal thinking
- diarrhoea, abdominal pain (stomach pain or discomfort)
- nausea, dyspepsia (indigestion)
- rash, pruritus (itching)
- fatigue (extreme tiredness)

Uncommon (may affect up to 1 in 100 people)
- lactic acidosis (build up of acid in your blood) in some cases involving motor weakness (weakness in your arms, legs or hands)
- gynaecomastia (breast enlargement in men)
- anorexia (loss of appetite), anxiety, emotional lability
- pancreatitis (inflammation of the pancreas), vomiting
- hepatitis (inflammation of the liver), jaundice (yellow of the skin or eyes)
- urticaria (itchy rash), arthralgia (joint pain)
- myalgia (aching muscles), asthenia (unusual tiredness or weakness)

Rare (may affect up to 1 in 1,000 people)
- anemia
- hyperglycaemia (high sugar levels in the blood)
- hepatic steatosis (fat in the liver)

Very rare (may affect up to 1 in 10,000 people)
- thrombocytopenia, neutropenia (blood disorders)
- diabetes mellitus
- motor weakness (most often reported in the setting of symptomatic hyperlacetatemia or lactic acidosis syndrome)
- liver failure

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zerit

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the bottle label and/or the blister after EXP. The expiry date refers to the last day of that month.

Store below 25°C (aclar/alu blisters).
Do not store above 30°C (HDPE bottles).
Store in the original package.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zerit contains
- The active substance is stavudine (30 mg).
- The other ingredients of the powder contained in the hard capsule are: lactose (180 mg), magnesium stearate, microcrystalline cellulose and sodium starch glycolate.
- The ingredients of the capsule shell are gelatine, iron oxide colorant (E172), silicon dioxide, sodium laurilsulphate and titanium dioxide colorant (E171).
- The capsule shells are marked using edible black printing ink containing shellac, propylene glycol, purified water, potassium hydroxide and iron oxide (E172).

What Zerit looks like and content of the pack
Zerit 30 mg hard capsules are light and dark orange and marked with “BMS 1966” on one side and “30” on the other side.
Zerit 30 mg hard capsules are supplied in blister packs of 56 hard capsules or bottles of 60 hard capsules. To help protect the capsules from excessive moisture, the bottle includes a desiccant canister.

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Package leaflet: Information for the user

Zerit 40 mg hard capsules
Stavudine

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  If you are taking didanosine, used to treat HIV infection.

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Before treatment with Zerit, you should have told your doctor:
- if you suffer from kidney disease or liver disease (such as hepatitis)
- if you have had peripheral neuropathy (persistent numbness, tingling, or pain in the feet and/or hands)
- if you have suffered from pancreatitis (inflammation of the pancreas).

Zerit can cause a sometimes fatal condition called lactic acidosis, together with an enlarged liver. This condition usually does not occur until a few months after onset of treatment. This rare, but very serious side effect occurs more often in women, particularly if very overweight. In addition, rare cases of liver failure/renal failure or fatal hepatitis have been reported.
Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver side effects and may require blood tests for control of liver function.

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- abdominal pain, nausea or vomiting
- rapid deep breathing, drowsiness (which may indicate pancreatitis, liver disturbance such as hepatitis, or lactic acidosis).

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Bone problems
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Other medicines and Zerit
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Zerit if you are taking didanosine, used to treat HIV infection.

Tell your doctor if you are taking any of the following medicines, as undesirable interactions may occur:
- zidovudine, used to treat HIV infection
  doxorubicin, used to treat cancer
  ribavirin, used to treat hepatitis C infection.

Zerit with food and drink
For maximum effect, Zerit should be taken on an empty stomach, and preferably at least one hour before a meal. If this is not possible, the capsules may also be taken with a light meal.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
You must contact your doctor to discuss the potential side effects and the benefits and risks of your antiretroviral therapy to you and your child. Lactic acidosis (sometimes fatal) has been reported in pregnant women who received Zerit in combination with other antiretroviral treatment.
If you have taken Zerit during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding
Tell your doctor if you are breast-feeding. It is recommended that HIV-infected women should not breast-feed under any circumstances in order to avoid transmission of HIV to the baby.

Driving and using machines
Zerit may cause dizziness and drowsiness.
If you are affected, do not drive and do not use any tools or machines.

Zerit contains lactose
These capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Zerit

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely as they will give you the best chance to delay development of a resistance to the medicinal product. Do not change the dose on your own. Continue to take this medicine until your doctor tells you otherwise.
For adults whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
To obtain optimal absorption, the capsules should be swallowed with a glass of water, preferentially at least one hour before a meal and on an empty stomach. If this is not possible, Zerit may also be taken with a light meal.
If you have problems swallowing capsules you should ask your doctor about the possibility of changing to the solution form of this medicine or you could carefully open the capsule and mix its contents with some food.

Use in children
For children whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
Children older than 3 months, whose body weight is less than 30 kg, should receive 1 mg/kg twice daily.

If you take more Zerit than you should
If you have taken too many capsules or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor or the nearest hospital for advice.

If you forget to take Zerit
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zerit
The decision to stop using Zerit should be discussed with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zerit, or those caused by any other medicines you may be taking at the same time, or by the complications of the infection. For this reason, it is important that you inform your doctor of any change in your health.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Treatment with stavudine (Zerit) often causes a loss of fat from legs, arms and face (lipoatrophy). This loss of body fat has been shown to be not fully reversible after discontinuation of stavudine. Your doctor should monitor for signs of lipoatrophy. Tell your doctor if you notice any loss of fat from your legs, arms, and face. When these signs occur, Zerit should be stopped and your HIV treatment changed.

Patients treated with Zerit have reported the following side effects:

Common (may affect up to 1 in 10 people)
- asymptomatic hyperlactatemia (build up of acid in your blood)
- lipoatrophy
- depression
- peripheral neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis (numbness, weakness, tingling or pain in the arms and legs)
- dizziness, abnormal dreams, headache
- insomnia (difficulty sleeping), somnolence (sleepiness), abnormal thinking
- diarrhoea, abdominal pain (stomach pain or discomfort)
- nausea, dyspepsia (indigestion)
- rash, pruritus (itching)
- fatigue (extreme tiredness)

Uncommon (may affect up to 1 in 100 people)
- lactic acidosis (build up of acid in your blood) in some cases involving motor weakness (weakness in your arms, legs or hands)
- gynaecomastia (breast enlargement in men)
- anorexia (loss of appetite), anxiety, emotional lability
- pancreatitis (inflammation of the pancreas), vomiting
- hepatitis (inflammation of the liver), jaundice (yellow of the skin or eyes)
- urticaria (itchy rash), arthralgia (joint pain)
- myalgia (aching muscles), asthenia (unusual tiredness or weakness)

Rare (may affect up to 1 in 1,000 people)
- anemia
- hyperglycaemia (high sugar levels in the blood)
- hepatic steatosis (fat in the liver)

Very rare (may affect up to 1 in 10,000 people)
- thrombocytopenia, neutropenia (blood disorders)
- diabetes mellitus
- motor weakness (most often reported in the setting of symptomatic hyperlacetatemia or lactic acidosis syndrome)
- liver failure

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zerit

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, the bottle label and/or the blister after EXP. The expiry date refers to the last day of that month.

Store below 25°C (aclar/alu blisters).
Do not store above 30°C (HDPE bottles).
Store in the original package.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zerit contains
- The active substance is stavudine (40 mg).
- The other ingredients of the powder contained in the hard capsule are: lactose (240 mg), magnesium stearate, microcrystalline cellulose and sodium starch glycolate.
- The ingredients of the capsule shell are gelatine, iron oxide colorant (E172), silicon dioxide, sodium laurilsulphate and titanium dioxide colorant (E171).
- The capsule shells are marked using edible black printing ink containing shellac, propylene glycol, purified water, potassium hydroxide and iron oxide (E172).

What Zerit looks like and content of the pack
Zerit 40 mg hard capsules are dark orange and marked with “BMS 1967” on one side and “40” on the other side.
Zerit 40 mg hard capsules are supplied in blister packs of 56 hard capsules or bottles of 60 hard capsules. To help protect the capsules from excessive moisture, the bottle includes a desiccant canister.

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

Zerit 200 mg powder for oral solution
Stavudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zerit is and what it is used for

Zerit belongs to a particular group of antiviral medicines, also known as antiretrovirals, called nucleoside reverse transcriptase inhibitors (NRTIs).

These are used to treat Human Immunodeficiency Virus (HIV) infection.

This medicinal product, in combination with other antiretrovirals, reduces the HIV viral load and keeps it at a low level. It also increases CD4 cell counts. These CD4 cells play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Zerit varies between patients. Your doctor will therefore be monitoring the effectiveness of your treatment.

Zerit may improve your condition, but it is not a cure for your HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy.Discuss with your doctor the precautions needed to avoid infecting other people.
During treatment, other infections, linked to a weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. What you need to know before you take Zerit

Do not take Zerit
- If you are allergic to stavudine or any of the other ingredients of this medicine (listed in section 6). Contact your doctor or pharmacist for advice.
  If you are taking didanosine, used to treat HIV infection

Warnings and precautions
Talk to your doctor before taking Zerit.
Before treatment with Zerit, you should have told your doctor:
- if you suffer from kidney disease or liver disease (such as hepatitis)
- if you have had peripheral neuropathy (persistent numbness, tingling, or pain in the feet and/or hands)
- if you have suffered from pancreatitis (inflammation of the pancreas).

Zerit can cause a sometimes fatal condition called lactic acidosis, together with an enlarged liver. This condition usually does not occur until a few months after onset of treatment. This rare, but very serious side effect occurs more often in women, particularly if very overweight. In addition, rare cases of liver failure/renal failure or fatal hepatitis have been reported.
Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver side effects and may require blood tests for control of liver function.

If you develop one of the following, contact your doctor:
- persistent numbness, tingling or pain in feet and/or hands (this may indicate the beginning of peripheral neuropathy, an adverse effect on the nerves), muscular weakness
- abdominal pain, nausea or vomiting
- rapid deep breathing, drowsiness (which may indicate pancreatitis, liver disturbance such as hepatitis, or lactic acidosis).

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately. In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

During therapy with Zerit there is often a gradual loss of subcutaneous fat (fat found beneath the skin), which is most notable in the face and on the legs and arms. Contact your doctor if you notice such changes.

Bone problems
Some patients taking Zerit may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pain (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Other medicines and Zerit
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Zerit if you are taking didanosine, used to treat HIV infection.

Tell your doctor if you are taking any of the following medicines, as undesirable interactions may occur:
- zidovudine, used to treat HIV infection
- doxorubicin, used to treat cancer
- ribavirin, used to treat hepatitis C infection.

Zerit with food and drink
For maximum effect, Zerit should be taken on an empty stomach, and preferably at least one hour before a meal. If this is not possible, Zerit may also be taken with a light meal.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy
You must contact your doctor to discuss the potential side effects and the benefits and risks of your antiretroviral therapy to you and your child. Lactic acidosis (sometimes fatal) has been reported in pregnant women who received Zerit in combination with other antiretroviral treatment.
If you have taken Zerit during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding
Tell your doctor if you are breast-feeding. It is recommended that HIV-infected women should not breast-feed under any circumstances in order to avoid transmission of HIV to the baby.

Driving and using machines
Zerit may cause dizziness and drowsiness.
If you are affected, do not drive and do not use any tools or machines.

Zerit contains sucrose and preservatives
After reconstitution with water, the solution contains 50 mg of sucrose per ml of solution. This should be taken into account in patients with diabetes mellitus. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. May be harmful to the teeth.
This product contains methylhydroxybenzoate (E218) and propylhydroxybenzoate (E216) that may cause allergic reactions (possibly delayed).

3. How to take Zerit

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Your doctor has defined your daily dose based on your weight and individual characteristics. Please follow these recommendations closely as they will give you the best chance to delay development of a resistance to the medicinal product. Do not change the dose on your own. Continue to take this medicine until your doctor tells you otherwise.
For adults whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).

To obtain optimal absorption, Zerit should be taken at least one hour before a meal and on an empty stomach. If this is not possible, Zerit may also be taken with a light meal.
Prepare the ready-to-use solution by mixing the powder with 202 ml of water or by slowly adding water up to the top edge of the bottle label shown by the arrow fill marks. Then screw the cap on tightly and shake the bottle well until the powder dissolves completely, and take or dispense the solution with the measuring cup provided. For infants who require a dose less than 10 ml, ask your pharmacist for a syringe to use to accurately measure the oral dose. Do not worry if the solution remains slightly hazy after mixing with water; this is normal. If needed, consult your pharmacist for help with this procedure.

Use in children

For children whose body weight is 30 kg or more, the usual starting dose is 30 or 40 mg given twice daily (with approximately 12 hours between each dose).
Children from birth to 13 days old should receive 0.5 mg/kg twice daily. Children at least 14 days old whose body weight is less than 30 kg, should receive 1 mg/kg twice daily.

If you take more Zerit than you should
If you have taken too much of the solution, or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor or the nearest hospital for advice.

If you forget to take Zerit
If you accidentally miss a dose, then simply take your normal dose when the next one is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking Zerit
The decision to stop using Zerit should be discussed with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When treating HIV infection it is not always possible to differentiate between unwanted effects caused by Zerit or those caused by any other medicines you may be taking at the same time, or by the complications of the infection. For this reason, it is important that you inform your doctor of any change in your health.

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Treatment with stavudine (Zerit) often causes a loss of fat from legs, arms and face (lipoatrophy). This loss of body fat has been shown to be not fully reversible after discontinuation of stavudine. Your doctor should monitor for signs of lipoatrophy. Tell your doctor if you notice any loss of fat from your legs, arms, and face. When these signs occur, Zerit should be stopped and your HIV treatment changed.

Patients treated with Zerit have reported the following side effects:

Common (may affect up to 1 in 10 people)
- asymptomatic hyperlactatemia (build up of acid in your blood)
- lipoatrophy
- depression
- peripheral neurologic symptoms including peripheral neuropathy, paresthesia, and peripheral neuritis (numbness, weakness, tingling or pain in the arms and legs)
- dizziness, abnormal dreams, headache
- insomnia (difficulty sleeping), somnolence (sleepiness), abnormal thinking
- diarrhoea, abdominal pain (stomach pain of discomfort)
- nausea, dyspepsia (indigestion)
- rash, pruritus (itching)
- fatigue (extreme tiredness)

Uncommon (may affect up to 1 in 100 people)
- lactic acidosis (build up of acid in your blood) in some cases involving motor weakness (weakness in your arms, legs or hands)
- gynaecomastia (breast enlargement in men)
- anorexia (loss of appetite), anxiety, emotional lability
- pancreatitis (inflammation of the pancreas), vomiting
- hepatitis (inflamation of the liver), jaundice (yellow of the skin or eyes)
- urticaria (itchy rash), arthralgia (joint pain)
- myalgia (aching muscles), asthenia (unusual tiredness or weakness)

Rare (may affect up to 1 in 1,000 people)
- anemia
- hyperglycaemia (high sugar levels in the blood)

- hepatic steatosis (fat in the liver)

Very rare (may affect up to 1 in 10,000 people)
- thrombocytopenia, neutropenia (blood disorders)
- diabetes mellitus
- motor weakness (most often reported in the setting of symptomatic hyperlacetatemia or lactic acidosis syndrome)
- liver failure

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zerit

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and on the carton after EXP. The expiry date refers to the last day of that month.

Do not store the dry powder above 30°C. Store in the original package in order to protect from excessive moisture.
The prepared oral solution is stable for 30 days in a refrigerator (2°C -8°C).
Keep the bottle tightly closed.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zerit contains
- The active substance is stavudine (200 mg).
- The other ingredients of the powder are: cherry flavour, methylhydroxybenzoate (E218), propylhydroxybenzoate (E216), silicon dioxide, simethicone, sodium carmellose, sorbic acid, stearate emulsifiers and sucrose.

What Zerit looks like and content of the pack
The powder contains 200 mg stavudine. The reconstituted solution contains 1 mg of stavudine per ml. Before reconstitution the Zerit powder appears as off-white to pale-pink, gritty powder. When reconstituted with 202 ml of water, produces 210 ml of a colorless to slightly pink, hazy solution. Zerit 200 mg powder for oral solution is supplied in a bottle containing 200 ml solution.

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